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Density and Dichotomous Family History Measures of Alcohol Use Disorder as Predictors of Behavioral and Neural Phenotypes: A Comparative Study Across Gender and Race/Ethnicity

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Background: Family history (FH) is an important risk factor for the development of alcohol use disorder (AUD). A variety of dichotomous and density measures of FH have been used to predict alcohol outcomes; yet, a systematic comparison of these FH measures is lacking. We compared 4 density and 4 commonly used dichotomous FH measures and examined variations by gender and race/ethnicity in their associations with age of onset of regular drinking, parietal P3 amplitude to visual target, and likelihood of developing AUD.

Methods: Data from the Collaborative Study on the Genetics of Alcoholism (COGA) were utilized to compute the density and dichotomous measures. Only subjects and their family members with DSM-5 AUD diagnostic information obtained through direct interviews using the *Semi-Structured Assessment for the Genetics of Alcoholism* (SSAGA) were included in the study. Area under receiver operating characteristic curves were used to compare the diagnostic accuracy of FH measures at classifying DSM-5 AUD diagnosis. Logistic and linear regression models were used to examine associations of FH measures with alcohol outcomes.

Results: Density measures had greater diagnostic accuracy at classifying AUD diagnosis, whereas dichotomous measures presented diagnostic accuracy closer to random chance. Both dichotomous and density measures were significantly associated with likelihood of AUD, early onset of regular drinking, and low parietal P3 amplitude, but density measures presented consistently more robust associations. Further, variations in these associations were observed such that among males (vs. females) and Whites (vs. Blacks), associations of alcohol outcomes with density (vs. dichotomous) measures were greater in magnitude.

Conclusions: Density (vs. dichotomous) measures seem to present more robust associations with alcohol outcomes. However, associations of dichotomous and density FH measures with different alcohol outcomes (behavioral vs. neural) varied across gender and race/ethnicity. These findings have great applicability for alcohol research examining FH of AUD.

Key Words: Alcohol Use Disorder, Family History, P300, Endophenotype, Risk and Development.

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FAMILY HISTORY (FH) of alcohol use disorder (AUD) has been consistently shown to be a major risk factor for developing AUD (Bohman et al., 1987; Cadoret et al., 1980; Dawson et al., 1992; Goodwin et al., 1974; Polich et al., 1994; Porjesz et al., 2005; Prescott et al., 2005; Rangaswamy et al., 2007). Ample evidence shows that FH is a robust predictor of alcohol problems and is associated with psychological and neurobiological precursors for AUD (Hill and O'Brien, 2015; Nurnberger et al., 2004; Porjesz et al., 2005). For example, FH is linked to greater risk for earlier initiation of drinking (Dawson, 2000; Hill and Yuan, 1999), increased frequency of alcohol intoxication (Pilatti et al., 2013), early onset of AUD (Lieb et al., 2002), and a higher prevalence of lifetime alcohol dependence across age, gender, and race (National Longitudinal Alcohol Epidemiological Survey, 2002). Additionally, FH has also been associated with aberrant electrophysiologic characteristics such as low P3/P300 (an event-related brain potential; ERP) amplitude in response to target stimuli, often considered as a biomarker of vulnerability for AUD (Begleiter et al., 1984; Begleiter et al., 1987; Cservenka, 2016; Hill et al., 1991; Hill et al., 2009; Porjesz et al., 2005). Indeed, several studies have demonstrated that low P3 amplitude appears to be independent of disease state and varies in individuals with a FH of AUD compared to controls from non-AUD families (Euser et al., 2012; Hill and O'Brien, 2015; Porjesz et al., 1998).

Given the importance of FH in alcohol research, increased attention has been given to its measurement and clinical applications. However, there exists a large degree of variability in the ascertainment and measurement of FH and the relative performance of different FH measures as predictors of phenotypes and endophenotypes, especially across different groups, has not been investigated. This is important because several variants of FH have been utilized to examine associations with numerous alcohol variables with little understanding of the differences in their predictive value across diverse ethnic and social groups. Moreover, population characteristics (i.e., cultural and societal factors) have been shown to affect alcohol use and problems with significant variability observed across gender and race/ethnicity (Berkman and Kawachi, 2000; Rehm et al., 2009; Substance Abuse and Mental Health Services Administration, 2015). Yet, little is known about how different FH measures and their associations with alcohol variables differ across gender and race/ethnicity.

More specifically, a study systematically comparing different FH measures, their associations with different alcohol outcomes, across gender and race/ethnicity, is important for the following reasons:

Variability in Measurement of FH (Dichotomous vs. Density)

The commonly used FH measures of AUD fall under *dichotomous* or *density* measures. *Dichotomous* measures

often categorize individuals as FH+ and FH− defined by the presence or absence of an AUD in the father/mother and/or among first- and/or second-degree relatives (Cservenka and Nagel, 2012; Schuckit and Smith, 1996). On the other hand, *density* measures are more complex scores that account for the number and type of family members who have the disorder. Several variants of density measures such as the *Family Expression of Alcoholism* (Zucker et al., 1994), the *FH Density* (Stoltenberg et al., 1998), and other alternatives (e.g., Cservenka and Nagel, 2012) have been used in extant research. Despite such variability in measurement of FH, very few studies have examined the comparative utility of dichotomous and density measures.

Variability in Ascertainment Methods (Direct vs Indirect)

Differences also exist in the methods used for ascertaining FH. Most often, information about family members is gathered either by directly interviewing each family member (*direct FH method*) or by having assessed family members report the alcohol use problems of unassessed family members (*indirect FH method*). Importantly, variations in ascertainment methods also affect the criteria used for determining affectedness of family members. For example, in the *direct FH method*, family members are directly interviewed using instruments such as the *Semi-Structured Assessment for the Genetics of Alcoholism* (SSAGA) (Bucholz et al., 1994), in which the diagnostic criteria, as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM; e.g., DSM-IV/DSM-5), are already incorporated into the instrument. Whereas, in the *indirect FH method*, instruments such as the *Family History Assessment Module* (FHAM) (Rice et al., 1995) are used where a relative's affectedness is decided based on predetermined criteria—a family member has to be named by 3 or more family members to be considered “affected.”

Variability in Coding Criteria

FH measures also vary in the use of coding criteria. For example, some FH measures have used the diagnostic criteria from clinical instruments (e.g., DSM) to create a binary coding of affectedness (i.e., 0 = unaffected, 1 = affected) while others have categorized affectedness into multiple categories that have then been collapsed to a binary code (e.g., Powers et al., 2017). Moreover, because studies have been carried out in the context of the evolution of diagnostic criteria over time, results of clinical instruments often correspond to different revisions of the DSM, with earlier studies defining AUD by DSM-III-R and DSM-IV. Very few studies to our knowledge have used DSM-5 to define affectedness in FH measures. Therefore, given the different versions of clinical instruments, criteria, and definitions that have been employed for coding affectedness, a systematic comparison

of FH measures is difficult, especially because they do not map perfectly onto each other.

Associations With AUD and Related Phenotypes

Studies comparing the predictive value and utility of different FH measures have largely examined their associations with behavioral phenotypes (e.g., tolerance and withdrawal) (Milne et al., 2013; Stoltenberg et al., 1998) and have mostly ignored their associations with endophenotypes. Endophenotypes are intermediate phenotypes on the putative causal pathway from genotype to phenotype (Euser et al., 2012). For example, low P3 amplitude, an ERP to a target of significance, has been considered as both a disease and vulnerability marker. Nevertheless, whether any differences exist in the associations between P3 amplitude and different variants of FH measures is not well-known. A comparative study of associations between different FH measures and P3 amplitude is important for the following reasons: (i) *Reduced P3 is considered a biomarker of risk for developing AUD*. There is substantial evidence that individuals with AUD, their unaffected offspring, and relatives manifest low P3 amplitude, particularly in multiplex AUD families compared to individuals with and without AUD from non-AUD families (Begleiter et al., 1984; Berman et al., 1993; Hesselbrock et al., 2001; Hill and Steinhauer, 1993b; Hill et al., 1999; Porjesz and Begleiter, 1996; Porjesz et al., 1998). (ii) *Reduced P3 is heritable and can be a familial risk*. Indeed, evidence shows that P3 amplitude recorded during a visual oddball paradigm is directly related to the number of first-degree alcoholic relatives and *not* the drinking history of an alcoholic or high-risk individual (Benegal et al., 1995; Cohen et al., 1994; Pfefferbaum et al., 1991; Porjesz et al., 2005). Moreover, supporting the notion that P3 is heritable, twin studies have shown that identical twins manifest more similar P3 amplitudes than unrelated individuals, with a metaheritability (via aggregating twin correlations across 5 studies) of 60% (van Beijsterveldt and van Baal, 2002; O'Connor et al., 1994; Steinhauer et al., 1987). Additionally, Carlson and colleagues (2004) have shown that P3 amplitude in nonalcoholic adolescent twin pairs who become discordant for AUD as adults also present reduced P3 amplitude, supporting the notion that this risk is familial. Further, Perlman and colleagues (2009) have shown that low P3 amplitude indexes risk for AUD, independent of any deleterious effect of alcohol use. However, despite extensive evidence linking FH of AUD to low P3 amplitude, it is unclear which measures (e.g., dichotomous or density) of FH are more predictive of this significant biomarker of risk for AUD. (iii) *Variability in P3 across gender and race/ethnicity*. The relationship between low P3 amplitude and the heritability of AUD may be subject to modulation by population differences and gender (Ehlers et al., 2003; Euser et al., 2011). Therefore, these points attest to the importance of testing the associations of different FH measures with P3 amplitude and variations in these associations across gender and race/ethnicity.

Gender and Race/Ethnic Differences

Substantial evidence shows that women and men differ in rates of alcohol use initiation, consequences of use, maintenance of use patterns, and attempts to stop and success at cessation (Keyes et al., 2008). Additionally, psychosocial factors may have different structural associations with AUD in men and women (Meyers et al., 2017; Schulte et al., 2009). Importantly, inconsistent findings across studies have been reported that may be attributed to the use of different measures of FH. For example, some studies have reported significant interactions between gender and FH, such that FH + males were especially more vulnerable to high levels of alcohol consumption (Barthwell, 1995). In other work, measures of SES (e.g., education, income) were shown to be more important predictors of alcohol dependence symptoms among men, whereas FH was a stronger predictor among women (LaBrie et al., 2010).

Similarly, aspects of race/ethnic group membership have been shown to mitigate or exacerbate the magnitude of alcohol-related outcomes (Gilman et al., 2008). For example, Whites tend to consume more alcohol than Blacks (Johnston et al., 2011) but Blacks reportedly have higher levels of alcohol problems (Zapolski et al., 2014). Yet, the risk for alcohol dependence associated with FH + seems to increase with age in Whites but decrease with age in Blacks (Russell et al., 1990). Importantly, whether associations between different FH measures and alcohol-related phenotypes vary across gender and race/ethnicity, particularly comparing Whites and Blacks, is less understood. Therefore, a comparative study of associations of different FH measures with AUD risk factors and their variation by gender and race/ethnicity is important.

Present Study

The aims of the present study are as follows: (i) to compare the associations of different FH measures (dichotomous and density) with behavioral and neural phenotypes of risk for AUD and (ii) to examine whether these associations vary across gender (between males and females) and race/ethnicity (between Whites and Blacks). We utilized data from the Collaborative Study on the Genetics of Alcoholism (COGA), a large, multisite, and multigenerational family study consisting of ethnically diverse AUD and community control families. COGA data comprise extensive assessments of individual family members with deep phenotyping in multiple domains (e.g., clinical, behavioral, neurophysiological). Also, information regarding each individual family member's alcohol use, related behaviors, DSM-5 AUD symptom counts, and diagnoses has been acquired through direct interviews using the SSAGA, a polydiagnostic psychiatric interview (Bucholz et al., 1994; Hesselbrock et al., 1999). These first-hand reports allow for greater reliability of the ascertained affectedness information and of FH measures derived from these reports. Therefore, taking advantage of

COGA's rich multimodal AUD data, large ethnically diverse sample, and diagnostic information obtained via direct interviews, we computed 4 commonly used dichotomous and 4 density measures of FH, compared their predictive value in associations with alcohol-related clinical, behavioral, and neural outcomes, across gender and race/ethnicity. Specifically, we examined the diagnostic accuracy of dichotomous and density FH measures at classifying DSM-5 AUD diagnosis, their associations with likelihood of AUD, age of onset of regular drinking, and parietal P3 amplitude to visual target stimuli. We also examined whether the diagnostic accuracy of these FH measures and their associations with the outcomes varied by gender (females vs. males) and self-reported race/ethnicity (Blacks vs. Whites).

MATERIALS AND METHODS

Sample Characteristics

Data are from the COGA study, which has been described in detail elsewhere (Begleiter et al., 1999; Nurnberger and Wiegand, 2011). To date, COGA has assessed data on alcohol use frequency, AUD symptom counts, and diagnoses for approximately 17,762 individuals belonging to 2,255 families. COGA's sample is well-suited for undertaking a systematic comparison of FH measures as its multiplex family data allow for use of the same subjects' familial information to compute and compare the utility of the 2 types of FH measures. Also, given that the sample size is large and ethnically diverse, a systematic comparison of the FH measures across gender and race/ethnicity is feasible.

Importantly, to compute the dichotomous and density measures of FH using COGA family data, we applied 2 inclusion criteria. (i) The subject and at least one of their family members had to have DSM-5 AUD symptom count and diagnostic information. (ii) The diagnostic information must be assessed using only direct interviews. That is, only those subjects and their relatives, whose affectedness information was gathered through the administration of the SSAGA, were used for the analyses in this study. A total of 16,346 subjects ($M_{\text{age}} = 37.24$; $SD = 15.00$) from 1,934 families, each of which comprised between 2 and 84 family members ($M_{\text{FamMem}} = 15.51$; $SD = 13.80$), fulfilled these criteria (see Table 1 for details on sample characteristics). The kinship information among family members was self-reported by participants and cross-verified through other family members. That is, at the time of their assessment/direct interview, participants described their family members and the relationships among them, and when their family members were assessed/directly interviewed, they in turn verified these relationships.

Table 1. Sample Characteristics

Characteristic	Category	N	%
COGA sample	Subjects	16,346	100.00
Sex	Female	8,729	53.40
	Male	7,617	46.60
Race/Ethnicity (self-reported)	White	11,753	71.90
	Black	3,901	23.90
	Other	688	4.20
	Missing	4	0.02
Hispanic (self-reported)	No	15,161	92.80
	Yes	1,183	7.20
	Missing	2	0.01
DSM-5 AUD diagnosed	No	8,218	50.30
	Yes	8,125	49.70

Informed consent was obtained from all participants. For neurophysiological assessments, experimental protocols were approved by each study site's institutional review board. Further, participants were excluded from neurophysiological assessments, if they had positive breath-analyzer test and/or urine screen results; hepatic encephalopathy/cirrhosis of the liver; history of head injury, seizures, or neurosurgery; uncorrected sensory deficits; history/symptoms of psychoses; self-reported positive test result for human immunodeficiency virus; other acute/chronic medical illnesses that affect brain function; or psychotropic medications that affect electrophysiologic measurement. Accordingly, a total of 7,516 subjects ($M_{\text{ERPage}} = 32.55$; $SD = 13.26$) had P3 data that were used in this study.

Independent Variables

Dichotomous FH Scores. We calculated 4 dichotomous FH scores, akin to those that have been extensively used in previous studies. The FH scores were calculated based on (i) *the category of the family relative*, which included father, mother, either parent, and any first-degree relative and (ii) *the affectedness criterion* based on DSM-5 AUD lifetime diagnosis. Accordingly, for each subject, we computed 4 dichotomous FH scores: (i) father with DSM-5 AUD diagnosis ($FH_{\text{Father-AUD}_{\text{DX}}}$), (ii) mother with DSM-5 AUD diagnosis ($FH_{\text{Mother-AUD}_{\text{DX}}}$), (iii) either parent with DSM-5 AUD diagnosis ($FH_{\text{Parent-AUD}_{\text{DX}}}$), and (iv) any first-degree relative with DSM-5 AUD diagnosis ($FH_{\text{First-AUD}_{\text{DX}}}$).

Density FH Scores. We also computed 4 ratio scores of FH density (FHD_r). Briefly, the density measures accounted for the degree of relatedness of different categories of biological relatives, weighted based on their AUD affectedness. The mathematical formulations used for calculating these density measures are elaborated in the Appendix S1. Specifically, the density measures accounted for (i) *2 variations in the weighting scheme and inclusion of family members*. That is, the set of relatives included were either (a) primary and secondary nondescendants (e.g., parents, grandparents, parental siblings, full siblings, and half-siblings) (FHD_{rPSND}) or (b) all relatives, regardless of degree or direction of relatedness, including both predecessors and descendants (FHD_{rAR}); (ii) *2 variations in affectedness coding criteria*. That is, for coding family members' AUD affectedness, the 2 criteria were (a) DSM-5 AUD lifetime diagnosis (AUD_{DX}) and (b) DSM-5 AUD maximum symptom count (AUD_{MaxSxCnt}). For DSM-5 maximum symptom count, the maximum number of endorsed symptoms at any 1 assessment across multiple assessments was used. This variable was transformed by the natural logarithm of the symptom count plus 1 (i.e., $\ln(\text{count} + 1)$). Accordingly, for each subject, we computed 4 density FH scores: (i) primary and secondary nondescendants with DSM-5 AUD diagnosis ($FHD_{\text{rPSND-AUD}_{\text{DX}}}$), (ii) primary and secondary nondescendants with DSM-5 AUD maximum symptom count ($FHD_{\text{rPSND-AUD}_{\text{MaxSxCnt}}}$), (iii) all relatives with DSM-5 AUD diagnosis ($FHD_{\text{rAR-AUD}_{\text{DX}}}$), and (iv) all relatives with DSM-5 AUD maximum symptom count ($FHD_{\text{rAR-AUD}_{\text{MaxSxCnt}}}$).

Dependent Variables

DSM-5 AUD Lifetime Diagnosis. Information from subjects' SSAGA interview was used to classify AUD status. Specifically, interviewed subjects were coded as affected (1) or unaffected (0) based on whether they met lifetime criteria for DSM-5 AUD. That is, subjects who endorsed 2 or more criteria that clustered within a single 12-month period were diagnosed with AUD.

Age of Onset of Regular Drinking. This was the age at which subjects first reported drinking at least once a month for 6 months or more, in their SSAGA interview. Ample evidence suggests that

the earlier the age when drinking is initiated, the greater the risk of developing AUD (DeWit et al., 2000; Hawkins et al., 1997). Importantly, early initiation of drinking has been linked to FH of AUD (Varma et al., 1994).

Visual Parietal P3 Amplitude. We also examined the associations between the FH measures and the parietal P3 amplitude to target stimuli measured using the visual oddball paradigm. The visual oddball paradigm has been previously described (Cohen et al., 1994). Briefly, 3 types of visual stimuli are presented: target (the letter X), nontarget (squares), and novel (a different colored geometric figure) on each trial. Subjects are required to respond to the target stimulus by pressing a button as quickly as possible, but not at the expense of accuracy. A total of 35 target stimuli, 210 nontarget stimuli, and 35 novel stimuli trials were presented with the probabilities of occurrence of the trials being 12.5% for the target trials, 75% for nontarget trials, and 12.5% for novel trials. Trials with baseline-corrected amplitudes greater than 75 μ V were marked as artifact contaminated and not analyzed further. Subjects whose data did not contain a minimum of 20 artifact-free trials in each condition were not selected for analysis. The P3 amplitude used in this analysis was the peak amplitude to target at the midline parietal (Pz) electrode between 300 and 700 milliseconds after stimulus presentation.

Statistical Analyses

Descriptive and Comparative Statistics. Descriptive statistics were computed for all FH measures. Specifically, for density measures, independent *t*-tests were used to compare the mean density scores within gender and race/ethnic groups (defined by participant's self-report). Similarly, for dichotomous measures, parametric Pearson's chi-square tests were used to compare the proportions of FH+ within gender and race/ethnic groups.

Diagnostic Accuracy of FH Measures at Classifying DSM-5 AUD Diagnosis. Diagnostic accuracy is the ability of a measure/test to discriminate between the target condition/disorder and health. We used receiver operating characteristic (ROC) curves to graphically display *trade-off* between *sensitivity* (true positive rate) and *specificity* (true negative rate) of FH measures for their ability to predict a dichotomous outcome, here DSM-5 AUD diagnosis. We also used area under the ROC curve (AUC) as a global measure to compare diagnostic accuracy across the FH measures. A measure/test with perfect diagnostic accuracy has an AUC of 1.0, and an uninformative measure/test is no better than chance where AUC = 0.5 (50% probability/random chance) (Florkowski, 2008).

Logistic and Linear Regression Analyses. We ran separate logistic regression models with each of the FH measures as predictors along with assessment age, gender, and self-reported race/ethnicity, included as covariates. In all models, lifetime diagnosis of DSM-5 AUD was included as a binary outcome variable. For age of onset of regular drinking and parietal P3 amplitude, we ran separate linear regression models with each of the FH measures as predictors along with assessment age, gender, and self-reported race/ethnicity, included as covariates. Age of onset of regular drinking and parietal P3 amplitude for visual target stimuli were included as continuous outcome variables in respective models.

Gender and Race/Ethnic Differences

To examine variation by gender and race/ethnicity in associations of dichotomous and density FH measures with the alcohol variables, we ran all AUC analyses, linear, and logistic regression models, separately for males, females, Whites, and Blacks. In all regression models, analyzed separately for males and females, we included assessment age and self-reported race/ethnicity as

covariates, whereas, for all regression models, analyzed separately for Whites and Blacks, we included assessment age and gender as covariates. We also examined interactions between gender, race/ethnicity, and each of the FH measures across the outcomes. These findings are reported in the Appendix S1.

Correction for Multiple Test Comparisons

In all analyses, for multiple comparisons, we used Bonferroni-corrected *p*-values to determine statistical significance. That is, when comparing the 4 density measures separately across gender and race/ethnicity using independent *t*-tests, a *p*-value = 0.012 ($\alpha = 0.05/4$ comparisons) was used. The same corrected *p*-value = 0.012 was used when comparing the 4 dichotomous measures separately across gender and race/ethnicity using nonparametric chi-square tests. For AUC and regression analyses comparing dichotomous and density measures, a *p*-value = 0.006 ($\alpha = 0.05/8$ comparisons) was used. Similarly, for all AUC and regression models comparing dichotomous and density measures separately across gender and race/ethnicity, for each of the outcome variables, a *p*-value = 0.003 ($\alpha = 0.05/16$ comparisons) was used.

RESULTS

Overall, for all subjects, as shown in Table 2, the highest and lowest mean scores among density measures were observed for FHD_{rPSND}-AUD_{Dx} and FHD_{rAR}-AUD_{MaxSxCnt}, respectively. Among dichotomous measures, FH_{First}-AUD_{Dx} and FH_{Mother}-AUD_{Dx} yielded the highest and lowest proportions of FH + subjects.

Diagnostic Accuracy of Dichotomous and Density Measures at Classifying DSM-5 AUD Diagnosis

It is evident from the ROC curves shown in Fig. 1A that density measures present greater diagnostic accuracy at classifying AUD diagnosis compared to the ROC curves for dichotomous measures (Fig. 1B). As shown in Table 3, although AUC for all 8 FH measures was significantly greater than 50% probability, AUC for all dichotomous measures was closer to 50% probability, indicating poor diagnostic accuracy. FH_{First}-AUD_{Dx} and FHD_{rPSND}-AUD_{MaxSxCnt} had the highest AUC among dichotomous and density measures, respectively. Overall, density (vs.

Table 2. Descriptive Statistics for Density and Dichotomous FH Scores for All Subjects

Density measures	N	Mean	SD
FHD _{rPSND} -AUD _{Dx}	9,805	0.53	0.25
FHD _{rPSND} -AUD _{MaxSxCnt}	9,805	0.43	0.19
FHD _{rAR} -AUD _{Dx}	14,569	0.51	0.22
FHD _{rAR} -AUD _{MaxSxCnt}	14,569	0.41	0.17
Dichotomous measures	N	# (Yes)	% (Yes)
FH _{Father} -AUD _{Dx}	6,752	4,359	64.6
FH _{Mother} -AUD _{Dx}	9,593	3,219	33.6
FH _{Parent} -AUD _{Dx}	10,411	6,281	60.3
FH _{First} -AUD _{Dx}	12,164	10,257	84.3

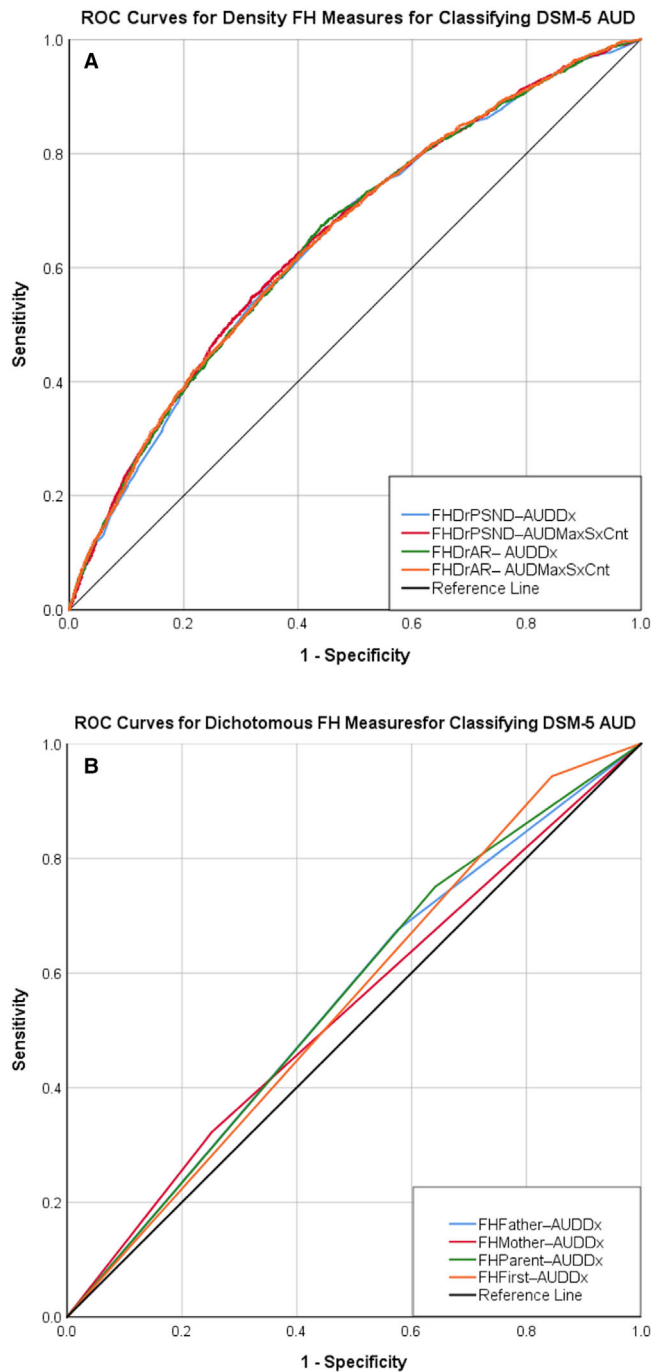


Fig. 1. The ROC curves displaying the trade-off between the sensitivity and the specificity for the 4 density measures (A) and the 4 dichotomous measures (B) in classifying DSM-5 AUD diagnosis.

dichotomous) measures presented higher AUC indicative of better predictive accuracy at classifying AUD diagnosis.

Associations of Dichotomous and Density Measures With Likelihood of AUD

As shown in Table 3, both dichotomous and density measures were significantly associated with likelihood of AUD.

That is, irrespective of whether FH is evaluated as a dichotomous or a density measure, it is associated with increased odds of AUD. Further, $FHD_{rPSND}-AUD_{MaxSxCnt}$ (OR = 20.45) and $FH_{First}-AUD_{Dx}$ (OR = 2.00) presented the most robust associations among density and dichotomous measures, respectively. Importantly, all density measures yielded higher coefficients and odds ratios thereby presenting improved predictive value over dichotomous measures.

Associations of Dichotomous and Density Measures With Age of Onset of Regular Drinking

As shown in Table 3, all dichotomous and density measures were significantly associated with age of onset of regular drinking. That is, irrespective of whether FH is evaluated as a dichotomous or a density measure, it is associated with early onset of regular drinking. Further, $FHD_{rPSND}-AUD_{MaxSxCnt}$ ($b = 3.05$) and $FH_{First}-AUD_{Dx}$ ($b = 0.78$) presented the most robust associations among density and dichotomous measures, respectively. Overall, compared to dichotomous measures, all density measures presented greater magnitude of associations with age of onset of regular drinking.

Associations of Dichotomous and Density Measures With Parietal P3 Amplitude

As shown in Table 3, all 4 density measures were significantly associated with P3 amplitude. That is, increases in density scores were associated with lower P3 amplitude. On contrary, among dichotomous measures, except $FH_{First}-AUD_{Dx}$, that failed to reach significance (following Bonferroni adjusted alpha), the rest were significantly associated, albeit the magnitude of their associations was modest. Further, $FHD_{rPSND}-AUD_{MaxSxCnt}$ ($b = 2.52$) and $FH_{Father}-AUD_{Dx}$ ($b = 1.03$) presented the most robust associations among density and dichotomous measures, respectively. Overall, density measures presented consistently greater magnitude of associations with P3 amplitude evidencing greater reliability over dichotomous measures.

Gender Differences

As shown in Table 4, among density measures, significant differences in mean scores between males and females were observed for $FHD_{rAR}-AUD_{Dx}$ and $FHD_{rAR}-AUD_{MaxSxCnt}$ measures. Specifically, females (vs. males) had higher mean scores. For dichotomous measures, no significant difference in the proportion of FH + males and females were observed.

Diagnostic Accuracy of FH Measures at Classifying DSM-5 AUD Diagnosis Across Gender. As shown in Table 5, in males, all 4 density measures presented significant diagnostic accuracy for classifying AUD diagnosis, with $FHD_{rPSND}-AUD_{MaxSxCnt}$ having the highest AUC. However, among dichotomous measures, $FH_{Mother}-AUD_{Dx}$ failed to be significantly different from 50% probability at classifying AUD

Table 3. Area Under the Curve and Unstandardized Beta Coefficients for Density and Dichotomous FH Measures From Logistic and Linear Regression Models for Each of the Alcohol Variables, Across All Subjects

FH measures	Diagnostic accuracy		Likelihood of AUD			Age of onset of regular drinking		P3 amplitude	
	N	AUC	N	b	OR	N	b	N	b
Density measures									
FHDr _{PSND} -AUD _{Dx}	9,805	0.64*	9,684	2.21*	9.13	7,749	-2.23*	5,254	-1.95*
FHDr _{PSND} -AUD _{MaxSxCnt}	9,805	0.65*	9,684	3.01*	20.45	7,749	-3.05*	5,254	-2.52*
FHDr _{AR} -AUD _{Dx}	14,566	0.62*	14,264	2.04*	7.71	11,456	-2.28*	6,894	-1.64*
FHDr _{AR} -AUD _{MaxSxCnt}	14,566	0.62*	14,264	2.85*	17.45	11,456	-2.98*	6,894	-2.12*
Dichotomous measures									
FH _{Father} -AUD _{Dx}	6,752	0.54*	6,696	0.58*	1.80	5,505	-0.74*	3,656	-1.05*
FH _{Mother} -AUD _{Dx}	9,593	0.52*	9,436	0.53*	1.71	7,607	-0.47*	5,106	-0.81*
FH _{Parent} -AUD _{Dx}	10,411	0.54*	10,231	0.60*	1.83	8,220	-0.55*	5,499	-0.94*
FH _{First} -AUD _{Dx}	12,164	0.55*	11,340	0.69*	2.00	9,184	-0.78*	6,157	-0.59

AUC, area under curve; OR, odds ratio.

* $p < 0.006$ (Bonferroni corrected).**Table 4.** Descriptive Statistics and Comparison of Density Scores Using Independent *t*-Tests and Dichotomous Scores Using Chi-square Tests, Across Gender

Density measures	Gender	N	Mean	SD	<i>t</i>
FHDr _{PSND} -AUD _{Dx}	Males	4,755	0.52	0.24	0.64
	Females	5,050	0.53	0.24	
FHDr _{PSND} -AUD _{MaxSxCnt}	Males	4,755	0.42	0.18	2.01
	Females	5,050	0.43	0.19	
FHDr _{AR} -AUD _{Dx}	Males	6,780	0.50	0.22	2.86*
	Females	7,789	0.51	0.22	
FHDr _{AR} -AUD _{MaxSxCnt}	Males	6,780	0.39	0.16	4.72*
	Females	7,789	0.41	0.16	
Dichotomous measures	Gender	N	#Yes	%Yes	χ^2
FH _{Father} -AUD _{Dx}	Males	3,375	2,164	64.1%	0.57
	Females	3,377	2,195	65.0%	
FH _{Mother} -AUD _{Dx}	Males	4,663	1,536	32.9%	1.54
	Females	4,930	1,683	34.1%	
FH _{Parent} -AUD _{Dx}	Males	5,062	3,072	60.7%	0.52
	Females	5,349	3,209	60.0%	
FH _{First} -AUD _{Dx}	Males	5,919	4,976	84.1%	0.56
	Females	6,245	5,281	84.6%	

t = independent *t*-test statistic. χ^2 = Pearson chi-square statistic.* $p < 0.012$ (Bonferroni corrected).

diagnosis. In males, other dichotomous measures, although significant, nevertheless presented diagnostic accuracy closer to 50% probability/chance, indicating poor diagnostic accuracy. Whereas, in females, all dichotomous and density measures presented significant diagnostic accuracy for classifying AUD diagnosis, albeit the dichotomous measures were again closer to 50% probability/chance, indicating poor diagnostic accuracy. Among density measures, FHDr_{PSND}-AUD_{MaxSxCnt} yielded the highest AUC and among dichotomous measures, FH_{Father}-AUD_{Dx}, FH_{Parent}-AUD_{Dx}, and FH_{First}-AUD_{Dx} presented equally high AUC. Overall, in both males and females, the density measures present consistently significant and higher diagnostic accuracy at classifying DSM-5 AUD diagnosis unlike dichotomous measures, which present high variability and poor diagnostic accuracy.

Associations of FH Measures With Likelihood of AUD Across Gender. As shown in Table 5, in males, all dichotomous and density measures were significantly associated with increased odds of AUD. Further, FHDr_{AR}-AUD_{MaxSxCnt} (OR = 15.86) and FH_{Father}-AUD_{Dx} (OR = 1.79) presented the most robust associations among density and dichotomous measures, respectively. In females too, all dichotomous and density measures were significantly associated with increased odds of AUD. Further, FHDr_{PSND}-AUD_{MaxSxCnt} (OR = 27.86) and FH_{First}-AUD_{Dx} (OR = 2.076) presented the most robust associations among density and dichotomous measures, respectively. Importantly, in both males and females, density (vs. dichotomous) measures seemed to be substantially more robust in their associations with likelihood of AUD.

Associations of FH Measures With Age of Onset of Regular Drinking Across Gender. As shown in Table 5, in males, all dichotomous and density measures were significantly associated with early onset of regular drinking. Further, FHDr_{AR}-AUD_{MaxSxCnt} ($b = -3.31$) and FH_{Father}-AUD_{Dx} ($b = -0.81$) presented the most robust associations among density and dichotomous measures, respectively. In females too, all dichotomous and density measures were significantly associated with early onset of regular drinking. FHDr_{PSND}-AUD_{MaxSxCnt} ($b = -3.87$) and FH_{Parent}-AUD_{Dx} ($b = -0.70$) presented the most robust associations among density and dichotomous measures, respectively. Importantly, in both males and females, all density (vs. dichotomous) measures presented associations of greater magnitude.

Association of FH Measures With Parietal P3 Amplitude Across Gender. As shown in Table 5, in males, all 4 density measures were significantly associated with low P3 amplitude. Further, FHDr_{PSND}-AUD_{MaxSxCnt} ($b = -3.26$) presented the most robust association. Among dichotomous measures, only FH_{Father}-AUD_{Dx} and FH_{Parent}-AUD_{Dx} presented significant associations. FH_{Father}-AUD_{Dx}

Table 5. Area Under the Curve and Unstandardized Beta Coefficients for Density and Dichotomous FH Measures From Logistic and Linear Regression Models for Each of the Alcohol Variables, Across Gender

FH measures	Diagnostic accuracy		Likelihood of AUD			Age of onset of regular drinking		P3 amplitude	
	N	AUC	N	b	OR	N	b	N	b
Males									
FHDr _{PSND} -AUD _{Dx}	4,755	0.63*	4,755	1.99*	7.345	3,955	-2.15*	2,546	-2.59*
FHDr _{PSND} -AUD _{MaxSxCnt}	4,755	0.64*	4,755	2.69*	14.855	3,955	-2.70*	2,546	-3.26*
FHDr _{AR} -AUD _{Dx}	6,778	0.62*	6,778	1.96*	7.135	5,716	-2.56*	3,242	-2.26*
FHDr _{AR} -AUD _{MaxSxCnt}	6,778	0.63*	6,778	2.76*	15.867	5,716	-3.31*	3,242	-2.98*
FH _{Father} -AUD _{Dx}	3,375	0.54*	3,375	0.58*	1.796	2,842	-0.81*	1,788	-1.34*
FH _{Mother} -AUD _{Dx}	4,663	0.50	4,663	0.51*	1.67	3,882	-0.39*	2,474	-1.03
FH _{Parent} -AUD _{Dx}	5,062	0.52*	5,062	0.51*	1.673	4,188	-0.43*	2,665	-1.03*
FH _{First} -AUD _{Dx}	5,919	0.55*	5,919	0.45*	1.577	4,712	-0.66*	2,980	-0.94
Females									
FHDr _{PSND} -AUD _{Dx}	5,050	0.66*	5,050	2.41*	11.231	3,794	-2.63*	2,708	-1.37
FHDr _{PSND} -AUD _{MaxSxCnt}	5,050	0.67*	5,050	3.32*	27.864	3,794	-3.87*	2,708	-1.86
FHDr _{AR} -AUD _{Dx}	7,788	0.63*	7,787	2.23*	9.314	5,740	-2.51*	3,652	-1.09
FHDr _{AR} -AUD _{MaxSxCnt}	7,788	0.63*	7,787	3.11*	22.588	5,740	-3.40*	3,652	-1.36
FH _{Father} -AUD _{Dx}	3,377	0.55*	3,377	0.52*	1.693	2,663	-0.68*	1,868	-0.75
FH _{Mother} -AUD _{Dx}	4,930	0.54*	4,929	0.59*	1.817	3,725	-0.55*	2,632	-0.62
FH _{Parent} -AUD _{Dx}	5,349	0.55*	5,348	0.58*	1.791	4,032	-0.70*	2,834	-0.86
FH _{First} -AUD _{Dx}	6,245	0.55*	6,244	0.73*	2.076	4,472	-1.13*	3,177	-0.26

AUC, area under curve; OR, odds ratio.

* $p < 0.003$ (Bonferroni corrected).

($b = -1.34$) was most robust. In females, interestingly, none of the dichotomous and density measures were associated with P3 amplitude. Overall, compared to dichotomous measures, albeit only in males, density measures were more consistently associated with P3 amplitude.

Race/Ethnic Differences

As shown in Table 6, significant differences in mean scores between Whites and Blacks were observed for all 4 density measures. Specifically, across all density measures, Whites (vs. Blacks) had higher mean scores. On the other hand, no significant difference in the proportions of FH + between Whites and Blacks were observed for FH_{Father}-AUD_{Dx} and FH_{Mother}-AUD_{Dx} measures. However, a significantly greater proportion of Whites (vs. Blacks) were FH + on FH_{Parent}-AUD_{Dx} and FH_{First}-AUD_{Dx} dichotomous measures.

Diagnostic Accuracy of FH Measures at Classifying DSM-5 AUD Diagnosis Across Race/Ethnicity. As shown in Table 7, in Whites, all dichotomous and density measures presented significant diagnostic accuracy at classifying AUD diagnosis. However, AUC of density measures was greater compared to dichotomous measures which were closer to 50% probability/chance. Further, FHDr_{PSND}-AUD_{MaxSxCnt} and FH_{Father}-AUD_{Dx} yielded the highest AUC among density and dichotomous measures, respectively. On the other hand, in Blacks, except for FH_{First}-AUD_{Dx}, all other dichotomous measures failed to be significantly different from random chance at classifying AUD diagnosis. In other words, those measures were completely uninformative. On

the contrary, in Blacks, all density measures presented significant diagnostic accuracy for classifying AUD diagnosis with FHDr_{PSND}-AUD_{MaxSxCnt} presenting the highest AUC. Therefore, in both Whites and Blacks, density measures presented consistent and significantly greater diagnostic accuracy for classifying AUD diagnosis, unlike dichotomous measures, which had poor diagnostic accuracy.

Associations of FH Measures With Likelihood of AUD Across Race/Ethnicity. As shown in Table 7, in Whites, all dichotomous and density measures were significantly associated with increased odds of AUD. Further, FHDr_{PSND}-AUD_{MaxSxCnt} (OR = 23.29) and FH_{First}-AUD_{Dx} (OR = 1.979) presented the most robust associations among density and dichotomous measures, respectively. In Blacks, all density measures were significantly associated with increased odds of AUD, being most robust for FHDr_{AR}-AUD_{MaxSxCnt} (OR = 7.81). However, among the dichotomous measures, only FH_{Mother}-AUD_{Dx} and FH_{Parent}-AUD_{Dx} presented significant associations. FH_{Mother}-AUD_{Dx} (OR = 1.51) yielded the most robust association. Importantly, in both Whites and Blacks, all density (vs. dichotomous) measures presented consistent and substantially robust associations with likelihood of AUD.

Associations of FH Measures With Age of Onset of Regular Drinking Across Race/Ethnicity. As shown in Table 7, in Whites, all dichotomous and density measures were significantly associated with early onset of regular drinking. Further, FHDr_{PSND}-AUD_{MaxSxCnt} ($b = -3.21$) and FH_{First}-AUD_{Dx} ($b = -0.93$) presented the most robust associations among density and dichotomous measures, respectively. In

Blacks, only $FHDr_{PSND-AUD_{Dx}}$ ($b = -1.61$) and $FHDr_{PSND-AUD_{MaxSxCnt}}$ ($b = -2.10$) density measures presented significant associations with the latter being most robust. Interestingly, all 4 dichotomous measures failed to present significant associations. Therefore, in both Whites and Blacks, density (vs. dichotomous) measures were more robust and consistent in their associations with age of onset of regular drinking.

Table 6. Descriptive Statistics and Comparison of Density Scores Using Independent *t*-Tests and Dichotomous Scores Using Chi-square Tests, Across Race/Ethnicity

Density measures	Race/Ethn	N	Mean	SD	<i>t</i>
$FHDr_{PSND-AUD_{Dx}}$	White	7,062	0.55	0.24	13.66*
	Black	2,302	0.47	0.23	
$FHDr_{PSND-AUD_{MaxSxCnt}}$	White	7,062	0.44	0.18	14.01*
	Black	2,302	0.38	0.18	
$FHDr_{AR-AUD_{Dx}}$	White	10,757	0.53	0.22	25.77*
	Black	3,193	0.43	0.19	
$FHDr_{AR-AUD_{MaxSxCnt}}$	White	10,757	0.42	0.16	27.16*
	Black	3,193	0.34	0.14	
Dichotomous measures	Race/Ethn	N	# (Yes)	% (Yes)	χ^2
$FH_{Father-AUD_{Dx}}$	White	5,358	3,458	64.5	0.25
	Black	1,127	736	65.3	
$FH_{Mother-AUD_{Dx}}$	White	6,986	2,332	33.4	1.98
	Black	2,150	753	35.0	
$FH_{Parent-AUD_{Dx}}$	White	7,484	4,692	62.7	50.45*
	Black	2,427	1,325	54.6	
$FH_{First-AUD_{Dx}}$	White	8,446	7,397	87.6	195.00*
	Black	3,163	2,439	77.1	

t = independent *t*-test statistic. χ^2 = Pearson chi-square statistic.

* $p < 0.012$ (Bonferroni corrected).

Associations of FH Measures With Parietal P3 Amplitude Across Race/Ethnicity. As shown in Table 7, in Whites, all 4 $FHDr$ measures were significantly associated with low P3 amplitude. Further, $FHDr_{PSND-AUD_{MaxSxCnt}}$ ($b = -0.38$) presented the most robust association. However, among dichotomous measures, only $FH_{Father-AUD_{Dx}}$ and $FH_{Parent-AUD_{Dx}}$ were significantly associated. Interestingly, in Blacks, none of the density or dichotomous measures except $FHDr_{PSND-AUD_{Dx}}$ were associated with P3 amplitude. Overall, compared to dichotomous measures, albeit only among Whites, associations of greater magnitude were observed for density measures.

DISCUSSION

In summary, all 4 density (vs. dichotomous) measures presented greater diagnostic accuracy in males, females, Whites, and Blacks. All 4 density (vs. dichotomous) measures presented robust associations with all 3 outcomes, especially in males and Whites. All 4 density (vs. dichotomous) measures were significantly associated with likelihood of AUD and age of onset of regular drinking in females and only with age of onset of regular drinking, in Blacks. These results corroborate previous findings that density measures of FH have greater predictive value. Nevertheless, the variations observed in the association of density and dichotomous FH measures with P3 amplitude, especially in females (vs. males) and Blacks (vs. Whites), indicate that utility of FH measures may differ depending on the phenotype and the social groups being studied.

Importantly, most studies investigating FH of AUD have focused on males, with data for females being less consistent,

Table 7. Area Under the Curve and Unstandardized Beta Coefficients for Density and Dichotomous FH Measures From Logistic and Linear Regression Models for Each of the Alcohol Variables, Across Race/Ethnicity

FH measures	Diagnostic accuracy		Likelihood of AUD			Age of onset of regular drinking		P3 amplitude	
	N	AUC	N	<i>b</i>	OR	N	<i>b</i>	N	<i>b</i>
Whites									
$FHDr_{PSND-AUD_{Dx}}$	7,062	0.64*	7,062	2.31*	10.09	5,846	-2.32*	3,543	-0.27*
$FHDr_{PSND-AUD_{MaxSxCnt}}$	7,062	0.65*	7,062	3.14*	23.29	5,846	-3.21*	3,543	-0.38*
$FHDr_{AR-AUD_{Dx}}$	10,756	0.61*	10,756	2.06*	7.86	8,836	-2.30*	4,733	-0.22*
$FHDr_{AR-AUD_{MaxSxCnt}}$	10,756	0.62*	10,756	2.93*	18.74	8,836	-3.05*	4,733	-0.29*
$FH_{Father-AUD_{Dx}}$	5,358	0.55*	5,358	0.60*	1.83	4,494	-0.83*	2,756	-0.13*
$FH_{Mother-AUD_{Dx}}$	6,986	0.52*	6,986	0.62*	1.86	5,792	-0.54*	3,455	-0.09
$FH_{Parent-AUD_{Dx}}$	7,484	0.54*	7,484	0.61*	1.84	6,175	-0.63*	3,671	-0.13*
$FH_{First-AUD_{Dx}}$	8,447	0.54*	8,447	0.68*	1.97	6,887	-0.93*	3,895	-0.10
Blacks									
$FHDr_{PSND-AUD_{Dx}}$	2,302	0.60*	2,302	1.47*	4.37	1,583	-1.61*	1,404	-0.30*
$FHDr_{PSND-AUD_{MaxSxCnt}}$	2,302	0.61*	2,302	2.05*	7.76	1,583	-2.10*	1,404	-0.30
$FHDr_{AR-AUD_{Dx}}$	3,192	0.58*	3,192	1.55*	4.74	2,177	-1.54	1,770	-0.28
$FHDr_{AR-AUD_{MaxSxCnt}}$	3,192	0.58*	3,192	2.06*	7.81	2,177	-1.55	1,770	-0.31
$FH_{Father-AUD_{Dx}}$	1,127	0.51	1,127	0.19	1.21	813	-0.29	714	-0.01
$FH_{Mother-AUD_{Dx}}$	2,150	0.50	2,150	0.41*	1.51	1,476	-0.24	1,336	-0.06
$FH_{Parent-AUD_{Dx}}$	2,427	0.51	2,427	0.33*	1.39	1,679	-0.28	1,486	-0.06
$FH_{First-AUD_{Dx}}$	3,163	0.54*	3,163	0.22	1.25	1,909	-0.35	1,898	-0.10

AUC, area under curve; OR, odds ratio.

* $p < 0.003$ (Bonferroni corrected).

suggesting a weaker effect (Hill et al., 1995; Hill and Steinhauser, 1993,b) previous studies using COGA data have shown lower P3 amplitude in female offspring from multiplex AUD families, *yet* to a lesser degree than in males (Porjesz and Begleiter, 1996; Porjesz et al., 1998). Indeed, a metaanalysis of 35 studies that investigated P3 amplitude in relation to FH of substance use disorder reported that in contrast to FH + males, low P3 amplitude is *not* present in FH + females (Euser et al., 2011). An alternative explanation for the absence of associations between FH measures and P3 amplitude, in females, may also be attributed to the physiological and social changes that seem to differentially affect males and females in their developmental stages, with males being more susceptible to problem drinking (Schulte et al., 2009). Similarly, considerable evidence shows that compared to Whites, Blacks report later initiation of drinking, lower rates and levels of use across almost all age-groups, *but* higher levels of alcohol problems than Whites (Zapolski et al., 2014). Nevertheless, studies have also shown that FH is significantly associated with lower P3 amplitudes in Blacks without being affected by current usage of alcohol. Therefore, it is important to identify how FH measures, psychosocial, cultural factors, and drinking norms may have race/ethnicity-specific influences on different alcohol outcomes (Hunte and Barry, 2012; Sartor et al., 2016).

Strengths and Implications

The present study has several strengths. *First*, to our knowledge, this is the first study to conduct a systematic comparison of the commonly used dichotomous FH measures with density measures and their associations with alcohol-related clinical (AUD diagnosis), behavioral (age of onset of regular drinking), and neural (P3 amplitude) phenotypes, and examine variations across gender and race/ethnicity. This systematic comparison enabled the discovery of diverse patterns of associations among different FH measures, alcohol outcomes, and diverse social groups. Importantly, the comparison of results across all subjects, males, females, Whites, and Blacks allows for testing the general and specific applicability of our findings. *Second*, to compute the dichotomous and density FH measures, we used subjects' FH information, alcohol use, AUD symptoms, and diagnosis obtained using *only* direct interviews. The validity of direct (vs. indirect) FH methods has been shown to be superior (Davies et al., 1997; Vandeleur et al., 2008), thereby ensuring reliability of our findings. *Third*, the density measures accounted for 2 variations in the inclusion of affected family members—in 1 variation, primary and secondary nondescendants were included, and in another, the entire extended family (all available relatives) was included. This allowed for encapsulating more familial information and allowed for testing if the predictive validity of FH increased/decreased when considering all available versus only the first- and second-degree relatives. The findings

suggest that inclusion of all relatives does not improve the predictive value of the FH measure. Indeed, the density measure— $FHDr_{PSND}-AUD_{MaxSxCnt}$ —based on primary and secondary nondescendants emerged as most consistently robust across alcohol outcomes and social groups. *Fourth*, contrary to existing studies (Milne et al., 2013; Stoltenberg et al., 1998) that have compared associations of different FH measures with alcohol and substance use symptoms and diagnoses (e.g., alcohol dependence), we examined associations of FH measures with important risk factors for the development of AUD. Importantly, ample evidence shows that *age of onset of regular drinking* is associated with increased alcohol problems during adult life and that *parietal P3 amplitude* is a biomarker for AUD risk. Given that FH is an index of risk that can be assessed early in individuals' lives, it is meaningful to examine its associations with risk factors that occur sooner in the stages of AUD development. Therefore, these findings can be of great value in informing the planning and development of early prevention and intervention strategies. *Lastly*, we took advantage of COGA's multimodal data that are available for a large and ethnically diverse sample with ~ equal numbers of males and females, allowing the comparison of FH measures and their associations with clinical, behavioral, and neural phenotypes, across gender, race/ethnicity, and in families with a range of density of FH of AUD, with substantial statistical power. Therefore, our findings may have great applicability in population-based contexts that examine FH of AUD.

Regardless of the findings in our study evidencing the important role of FH and the robustness of density over dichotomous FH measures in predicting alcohol outcomes, it is important to consider alternative explanations: (i) An individual's own alcohol use may affect the alcohol outcomes studied here, beyond the influence of one's FH. Although studies (e.g., Pfefferbaum et al., 1991) have shown that effect of FH on neurocognitive alcohol outcomes like P3 amplitude is above and beyond an individual's drinking history and that the effect of FH does not depend on an individual's drinking (e.g., Dager et al., 2015), it is nevertheless important for future studies to account for individuals' current alcohol use. (ii) Social determinants like low socioeconomic-status (SES) and parental education/income may affect the outcomes examined here, perhaps beyond the influence of FH. Indeed, studies show that although individuals from higher and lower SES may not differ in their alcohol consumption, the latter group is more affected by negative alcohol-related consequences further complicated by race/ethnicity and gender (Collins, 2016). Future studies examining effects of FH should also consider the influence of such social determinants. (iii) Lastly, because it is difficult to tease apart the extent of biological (e.g., genes) and psychosocial (e.g., rearing) influences of FH, the outcomes observed here may be due to the genetic transmission, psychosocial effects, or the interaction of both.

Strengths of Density FH Measures

Although we computed both dichotomous and density FH measures using familial data from the *same* COGA subjects and their family members, the strengths of density measures outweigh those of dichotomous measures for the following reasons: *First*, density measures are more comprehensive and incorporate contributions of alcohol-affected biologically related relatives, type of relatives (e.g., first- or second-degree), and degree of relatedness. Moreover, affectedness of family members was defined using 2 criteria (*DSM-5 AUD lifetime diagnosis* and *DSM-5 AUD maximum symptom count* at any 1 assessment). Importantly, using DSM-5 based maximum symptom count as an affectedness criterion, allowed for improving on previous measures in capturing the density of the FH more effectively. That is, given the possibility that some family members may *not* fulfill the diagnostic criteria for AUD but may nevertheless present at least 1 alcohol-related symptom, inclusion of relatives based on the maximum symptom count is meaningful and more informative. In doing so, the density of one's FH is more closely captured and the sensitivity of density measures as risk indices is increased even for individuals without any AUD-diagnosed relatives. Indeed, the density measure $FHD_{\text{PSND}-\text{AUD}_{\text{MaxSxCnt}}}$, based on log-transformed DSM-5 maximum symptom counts of primary and secondary non-descendants, emerged as the most informative measure with the highest diagnostic accuracy at classifying AUD diagnosis and with most robust associations with clinical, behavioral, and neural phenotypes, for all subjects. *Second*, the density measures used a weighting scheme that corresponded to the affected family members' degree of relatedness such that the weights decreased exponentially with the increase in degree of relatedness. This formulation was designed to also approximate the amount of biopsychosocial information shared between an individual and his/her affected relative. That is, the biological (genes) and psychosocial (environment) information shared between individuals and their siblings may be more similar than between an individual and a distant cousin. *Third*, because density measures are ratio/proportion scores, they control for inflation of scores due to variation in subjects' total number of alcohol-affected relatives. The benefit of using ratio scores, compared to the dichotomous measures which are nominal scores, is that they allow for a maximum potential score to always remain the same (i.e., 1) for all. Moreover, the algorithm used to generate the density measures counts the number of affected relatives and keeps the total weights of known relatives (denominator of the ratio score) constant (see Appendix S1). Therefore, even if the affectedness status of a relative were to be unknown, it does not contribute to the density score whatsoever.

Overall, our results corroborate findings from previous comparative studies that density measures are more advantageous FH measures as they contain higher resolution familial information compared to simple dichotomous measures.

Limitations

Despite the strengths and informativeness of the density measures over commonly used dichotomous measures, several limitations prevail. *First*, an important caveat is that these density measures may not be utilized by studies where information about biological relatives is not typically available, admittedly making the general applicability of these measures somewhat limited. *Second*, the AUC for density measures, while greater than those for dichotomous measures, was nevertheless low for diagnostic/screening contexts. Indeed, it has been observed that measures of diagnostic accuracy are very sensitive to the characteristics of the population in which the test accuracy is evaluated. Accordingly, in our analyses we show that diagnostic accuracy is substantially variable across groups, particularly for dichotomous measures. *Third*, more work is needed to express confidence in the diagnostic accuracy of an FH density score based on how many and which kind of relatives and their affectedness are known for a given individual. Moreover, it has been observed that some measures largely depend on the prevalence of the disorder/condition, while others are highly sensitive to the spectrum of the disorder/condition in the studied population. Indeed, Milne and colleagues (2013) have shown that for disorders with high (vs. low) prevalence (e.g., AUD, smoking), density (vs. dichotomous) measures should be preferred. *Fourth*, it has been seen that multiple substance use (e.g., nicotine, marijuana) in individuals with AUD with or without meeting criteria for substance use disorder is often observed as part of their clinical profile, including in the present sample. However, given the substantial sharing of familial vulnerability to alcohol *and* drug problems, along with evidence for cross-predictions, where a FH of drug problem predicts alcohol use/problems and a FH of alcohol problems predicts substance use/problems (e.g., Kendler et al., 2015), our findings may not be invalid. Nevertheless, future studies should investigate such polysubstance use effects. *Lastly*, density measures, like dichotomous/other FH measures, do not parse apart the effects of biological and psychosocial aspects in their measurement of FH. Although Zucker and colleagues (1994) included the extended family in their computation of FEA scores, they reasoned that it mostly represented genetic risk, while Stoltenberg and colleagues (1998) included only parents and grandparents in their FHD measure and reasoned that it represented biopsychosocial risk comprising biological effects (genes inherited from parents and grandparents) and psychosocial effects (rearing environment, with the assumption that individuals are most often reared by parents and grandparents). Yet, FH measures are *not* pure indices of genetic risk, but represent a complex combination of psychosocial family effects (rearing environment, family harmony, cohesion, etc.) that interact with one's molecular genetic risk. Therefore, the inclusion of more (vs. limited) relatives does not necessarily increase the genetic risk or undermine the psychosocial risk components in FH measures. Rather, including contributions from known family

members into the measurement of FH likely increases the informativeness of the role of FH for *both* aspects (biological and psychosocial). The COGA study has molecular genetic (polygenic risk scores for alcohol-related behaviors) as well as environmental measures (e.g., parental monitoring and family conflict) that will be utilized to address these issues in future studies.

Overall, density (vs. dichotomous) FH measures have greater potential for use as predictors in general alcohol-related research and in analyzing neural correlates of familial risk (low P3 amplitude). Density measures of FH are more informative and present greater utility for use as risk indices, albeit caution should be exercised in using variants of FH measures when gender and race/ethnicity are to be studied.

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CONFLICT OF INTEREST

All coauthors reported no financial interests or potential conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1 Supplementary analyses and findings.